17 Specific Target Organ Toxicity (Single or Repeated Exposure) – Subclass 6.9

Chapter contents

List of tables

17.1 General considerations

17.1.1 Specific target organ toxicity overview

See section 9.6 in chapter 9 for definitions of the key terms used in this chapter.

This subclass provides a means of classifying substances that produce specific target organ or systemic toxicity arising from single or repeated exposure. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included (other than those used to derive another classification).

Classification identifies the chemical substance as being a specific target organ or systemic toxicant, so it potentially presents adverse health effects in people who are exposed to it.

Classification depends on the availability of reliable evidence that single or repeated exposure to the substance has produced a consistent and identifiable toxic effect in humans or in experimental animals. This includes toxicologically significant changes that have affected the function or morphology of a tissue or organ, or have produced serious changes to the biochemistry or haematology of the organism. To be eligible for classification, these changes need to be relevant for human health.

Assessment should take into consideration not only significant changes in a single organ or biological system, but also generalised changes of a less severe nature involving several organs. Specific target organ or systemic toxicity can occur by any route that is relevant for humans; that is, principally oral, dermal, or inhalation.

Non-lethal toxic effects observed after a single-event exposure are also classified under subclass 6.9.

Specific toxic effects that are eligible for classification under class 6 or class 8 are assessed separately under the appropriate toxic endpoints and are not used to derive a subclass 6.9 classification. These effects are:

- acute lethality or toxicity (subclass 6.1 – see chapter 10);
- skin corrosivity (subclass 8.2) or irritation (subclass 6.3) (see chapter 11);
- eye corrosivity (subclass 8.3) or eye irritation (subclass 6.4) (see chapter 12);
- respiratory or contact sensitisation (subclass 6.5 – see chapter 13);
- carcinogenicity (subclass 6.7 – see chapter 14);
- mutagenicity (subclass 6.6 – see chapter 15); and
- reproductive toxicity (subclass 6.8 – see chapter 16).

17.1.2 Weight of evidence approach

The best quality data should be used as the fundamental basis for classification. Preferably, classification should be based on primary data sources. It is essential that test conditions be clearly and completely articulated.

Animal data from internationally harmonised test methods are preferred for classification under this subclass. Data should preferably be derived using Organisation for Economic Co-operation and Development Test Guidelines or equivalent according to the principles of Good Laboratory Practice. When such data are not available, classification should be based on the best available data using a weight-of-evidence approach.

See section 1.3 in chapter 1 for information about assessing data quality.

See Appendix 17A for a detailed list of acceptable test methods for specific target organ toxicity (single or repeated exposure).

17.2 Specific target organ toxicity (single or repeated exposure) hazard and classification criteria

17.2.1 Specific target organ toxicity (single or repeated exposure) effects threshold criteria

Schedule 4 to the Hazardous Substances (Minimum Degrees of Hazard) Regulations 2001 states:

2 Minimum degrees of hazard

(1) A substance with toxic properties is not hazardous for the purposes of the Act unless—

…

(s) data for the substance indicates, in the opinion of an expert, evidence of a significant adverse biological effect or a significant toxic effect (other than an effect referred to in any of paras (a) to (r)) on the function or morphology of an organ, or on the biochemistry or haematology of an organism or human being as a result of exposure to the substance and, in the case of a significant biological effect, the change is relevant to human health.

17.2.2 Specific target organ toxicity (single or repeated exposure) classification criteria for substances

Schedule 4 to the Hazardous Substances (Classification) Regulations 2001 identifies two classification categories for substances that are target organ toxicants (subclass 6.9).

- *Category 6.9A – substances that are toxic to human target organs or systems*

  (a) A substance for which data indicate to an expert evidence of a causal relationship between exposure of humans to the substance and the development of target organ or systemic toxicity that would not result in the substance being classified in any of subclasses 6.1 and 6.3–6.8.

  (b) A substance for which data indicate to an expert evidence of a significant adverse biological effect on the function or morphology of an organ or on the biochemistry or haematology of an organism as a result of exposure to the substance that would not result in the substance being classified in any of subclasses 6.1 and 6.3–6.8 and that are produced at low exposure concentrations and are of relevance to human health.

- *Category 6.9B – substances that are harmful to human target organs or systems*

  A substance for which data indicate to an expert evidence of a significant adverse biological effect on the function or morphology of an organ or on the biochemistry or haematology of an organism or human being as a result of exposure to the substance that would not result in the substance being classified in any of subclasses 6.1 and 6.3–6.8, and that are produced at moderate exposure concentrations and are of relevance to human health.

The classification criteria above are based on the Globally Harmonised System for Classification and Labelling (GHS) (United Nations, 2007). See Appendix 17C for a comparison of the HSNO Act and GHS criteria. See Appendix 17D for a comparison with the EU risk phrases for target organ toxicity.

17.2.3 Considerations for specific target organ toxicity (single or repeated exposure) classification

The relevant route of exposure by which the classified substance produces damage should be identified. Classification is determined by expert judgement, on the basis of the weight of all evidence available, including the guidance presented below.

A weight-of-evidence approach to all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ or systemic toxic effects that merit classification.

The information required to evaluate specific target organ toxicity (single exposure) comes from single exposure in humans (for example, exposure at home, in the workplace, or environmentally) or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies that can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues or organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

The information required to evaluate specific target organ toxicity (repeated exposure) comes from repeated exposure in humans (for example, exposure at home, in the workplace, or environmentally) or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28-day, 90-day, or lifetime studies (up to two years) that include haematological, clinicochemical, and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues or organs to be identified. Data from repeat-dose studies performed in other species may also be used. Other long-term exposure studies (for example, for carcinogenicity, neurotoxicity, or reproductive toxicity) may also provide evidence of specific target organ or systemic toxicity that could be used in the assessment of classification.

In exceptional cases, based on expert judgement, it may be appropriate to classify certain substances with human evidence of specific target organ or systemic toxicity as 6.9B when the weight of human evidence is not sufficiently convincing to warrant a 6.9A classification and/or based on the nature and severity of effects. Dose or concentration levels in humans should not be considered in the classification, and any available evidence from animal studies should be consistent with the 6.9B classification. In other words, if animal data are also available on the chemical that it warrants 6.9A classification, the chemical should be classified as 6.9A.

17.2.4 Effects considered to support classification

Reliable evidence associating single or repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for classification.

It is recognised that evidence from human experience and incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions (for example, information on dose and exposure to other substances or confounding factors that may have influenced the outcome). This evidence may not

provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

Evidence from appropriate studies in experimental animals can furnish much more detail than can be gained from human experience and incidents, in the form of clinical observations, and macroscopic and microscopic pathological examination (haematology and clinical chemistry for repeat dose studies). This can often reveal hazards that may not be life-threatening, but may indicate functional impairment. Consequently, all available evidence and relevance to human health must be taken into consideration in the classification process.

Relevant toxic effects in humans and/or animals are as follows.

- Morbidity resulting from single exposure.
- Morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses or concentrations, due to the bioaccumulation of the substance or its metabolites, or the accumulation of effect as a result of the detoxification process becoming overwhelmed by repeated exposure to the substance or its metabolites.
- Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (for example, sight, hearing, and smell).
- Any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters.
- Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination.
- Multifocal of diffuse necrosis, fibrosis, or granuloma formation in vital organs with regenerative capacity.
- Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (for example, severe fatty change in the liver).
- Evidence of appreciable cell death (including cell degeneration, severe acute tubular nephrosis in the kidney, ulcerative gastritis, and reduced cell numbers) in vital organs incapable of regeneration (for example, fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (for example, aplasia or hypoplasia of the bone marrow).

Effects that are not considered to support classification are:

- clinical observations or small changes in bodyweight gain, food consumption, or water intake that may have some toxicological importance, but that do not, by themselves, indicate ‘significant’ toxicity;
- small changes in clinical biochemistry, haematology, or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;
- changes in organ weight with no evidence of organ dysfunction;

- adaptive responses that are not considered toxicologically relevant;
- substance-induced species-specific mechanisms of toxicity demonstrated with reasonable certainty to be not relevant for human health; and
- local-only effects, after single-dose exposure, at the site of administration for the routes tested, especially when adequate testing by other principal routes show lack of specific target organ or systemic toxicity.

17.2.5 Guidance value ranges for single and repeat dose exposures

Specific target organ toxicity (single exposure)

To help to decide whether and to what extent (6.9A or 6.9B) a substance should be classified, dose–concentration 'guidance values' are provided in Table 17.1. These are the dose–concentration values that have been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose–concentration above which a degree of toxic effect is acknowledged.

Thus, in animal studies, when significant toxic effects are observed that indicate classification is necessary, consideration of the dose–concentration at which these effects were seen, in relation to the suggested guidance values, provides useful information to help to assess the need to classify (since the toxic effects are a consequence of the hazardous property or properties and the dose–concentration value).

The range of guidance values for single-dose exposure that has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 17.1.

These single dose–concentration values produce a significant non-lethal toxic effect, that is, they are not median lethal dose (LD_{50}) or median lethal concentration (LC_{50}) values. These values are not strict demarcation values, but should be used within a weight-of-evidence approach for deciding classification.

Table 17.1: Guidance value ranges for single dose exposures

		Guidance value ranges for category	
Route of exposure	**Units**	**6.9A**	**6.9B**
Oral (rat)	mg/kg bw	≤ 300	> 300 – 2,000
Dermal (rat or rabbit)	mg/kg bw	≤ 1,000	> 1,000 – 2,000
Inhalation (rat) gas	ppm	≤ 2,500	> 2,500 – 5,000
Inhalation (rat) vapour	mg/L	≤ 10	> 10 – 20
Inhalation (rat) dust, mist, fume	mg/L/4 hours	≤ 1.0	> 1.0 – 5.0

Note: L = litre; mg/kg bw = milligrams per kilogram of bodyweight; mg/L = milligrams per litre; ppm = parts per million.

Thus, it is feasible that a specific profile of toxicity is seen to occur at a dose–concentration below the guidance value, for example, < 2,000 milligrams per kilogram of bodyweight (mg/kg bw) by the oral route. However the nature of the effect may

result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value (for example, at or above 2,000 mg/kg bw by the oral route), but in addition there may be supplementary information from other sources (for example, other single-dose studies or human case experience), which supports a conclusion that, in view of the weight of evidence, classification would be prudent.

Specific target organ toxicity (repeated exposure)

In studies conducted in experimental animals, reliance on observation of effects alone (that is, without reference to the duration of experimental exposure and dose–concentration value), omits a fundamental concept of toxicology; that is, all substances are potentially toxic, and what determines the toxicity is a function of the dose–concentration and the duration of exposure. In most studies conducted in experimental animals the test guidelines use an upper limit dose value.

To help to decide whether and to what degree (6.9A or 6.9B) a substance should be classified, dose–concentration 'guidance values' are provided in Table 17.2. These are the dose–concentration values that have been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose–concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimise the test objective, so most studies will reveal some toxic effect at least at this highest dose. Therefore, what is to be decided is not only what effects have been produced, but also at what dose–concentration level and over what period were they produced and how relevant are they for humans.

Thus, in animal studies, when significant toxic effects are observed that would indicate classification is necessary, consideration of the duration of experimental exposure and the dose–concentration value at which these effects were seen, in relation to the suggested guidance values, provides useful information to help to assess the need to classify (since the toxic effects are a consequence of the hazardous property or properties, the duration of exposure, and the dose–concentration value).

The decision to classify can be influenced by the dose–concentration guidance values at or below which a significant toxic effect has been observed.

The guidance values proposed in Table 17.2 refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis from which to extrapolate equivalent guidance values for toxicity studies of longer or shorter duration, using a dose–exposure time extrapolation similar to Haber's rule for inhalation. This rule states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure.

The assessment should be done on a case-by-case basis; for example, for a 28-day study the guidance values in Table 17.2 would be increased by a factor of three. Thus, for 6.9A and 6.9B classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur at or below the (suggested) guidance values in the table would justify classification.

Table 17.2: Guidance value ranges for repeated dose exposures

		Guidance value ranges for category	
Route of exposure	**Units**	**6.9A**	**6.9B**
Oral (rat)	mg/kg bw	10	10–100
Dermal (rat or rabbit)	mg/kg bw	20	20–200
Inhalation (rat) gas	ppm/6 hours/day	50	50–250
Inhalation (rat) vapour	mg/L/6 hours/day	0.2	0.2–1.0
Inhalation (rat) dust, mist, fume	mg/L/6 hours/day	0.02	0.02–0.2

Note: L = litre; mg/kg bw = milligrams per kilogram of bodyweight; mg/L = milligrams per litre; ppm = parts per million.

The values and ranges in Table 17.1 and Table 17.2 are intended to be only guides; that is, they are to be used as part of the weight-of-evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values. These values are not no observed effect levels (NOELs), but are lowest observed adverse effect levels (LOAELs).

It is feasible that a specific profile of toxicity is seen to occur in repeat-dose animal studies at a dose–concentration level below the guidance value (for example, < 100 mg/kg bw/day by the oral route). However, the nature of the effect (for example, nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect) may result in a decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value (for example, at or above 100 mg/kg bw/day by the oral route) and with supplementary information from other sources (for example, other long-term administration studies or human case experience) supports a conclusion that, in view of the weight of evidence, classification would be prudent.

See Appendix 17B for converting a concentration of a substance in the diet (ppm) to a dietary intake (mg/kg bw/day).

17.2.6 Study duration

As stated above, the use of factors based on Haber's rule should take into account rat studies of a duration shorter than 90 days (3 months). A similar approach should be taken in a weight-of-evidence approach when assessing data from longer-term studies. This is not a strictly arithmetic approach, but a consideration of data close to the guideline values.

Similarly, when considering species other than rats, there is evidence that species generally differ in their response. A consideration in relation to the weight of evidence could be that mice are likely to respond at higher dose levels than are rats, while dogs are likely to respond at lower dose levels than are rats. Thus, a mouse study with an LOAEL in the range 100–200 mg/kg bw/day may be appropriate for classification (as 6.9B), while a dog study with a LOAEL in the range 50–100 mg/kg bw/day may not be appropriate for classification.

It is emphasised that these aspects should be considered in the overall determination of the weight of evidence for the classification, not as ‘rules’. Therefore, no guideline values are provided here.

17.2.7 Other considerations

When a substance is characterised only by use of animal data (typical of new chemicals, but also true for many existing chemicals), the classification process would include reference to dose–concentration guidance values as one of the elements that contribute to the weight-of-evidence approach.

When well-substantiated human data are available showing a specific target organ or systemic toxic effect that can be reliably attributed to repeated or prolonged exposure to a chemical substance, the substance may be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ or systemic toxicity was seen at or below the proposed dose–concentration guidance value for animal testing, and subsequent human incident data shows a specific target organ or systemic toxic effect, then the substance should be classified.

A substance that has not been tested for specific target organ or systemic toxicity may be classified on the basis of data from a validated structure activity relationship and an expert, judgement-based extrapolation from a structural analogue that has previously been classified, and with substantial support from a consideration of other important factors (such as the formation of common significant metabolites). This could include consideration of data from other routes such as injection.

17.3 Classification of mixtures

Mixtures are classified using the same criteria as for substances or as described below. As with substances, mixtures may be classified for specific target organ or systemic toxicity following a single exposure and/or repeated exposure.

17.3.1 Classification of mixtures when data are available for the complete mixture

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified using a weight-of-evidence evaluation of the data. Care should be exercised when evaluating data on mixtures that the dose, duration, observation, or analysis does not render the results inconclusive.

17.3.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

When the mixture itself has not been tested to determine its specific target organ or systemic toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data can be used in accordance with the following bridging principles. This ensures the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without needing additional testing in animals.

(a) Dilution

If a mixture is diluted with a diluent that has the same or a lower toxicity classification as the least toxic original ingredient and is not expected to affect the toxicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

(b) Batching

The toxicity of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product, where produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the batch has changed. If the latter occurs, a new classification is necessary.

(c) Concentration of highly toxic mixtures

If, in a mixture classified 6.9A, the concentration of a toxic ingredient is increased, the concentrated mixture should remain classified as 6.9A without additional testing.

(d) Interpolation within one toxicity category

For three mixtures with identical ingredients, where mixtures A and B are in the same toxicity category and mixture C has the same toxicologically active ingredients with concentrations intermediate to the concentrations of those ingredients in mixtures A and B, then mixture C is assumed to be in the same toxicity category as mixtures A and B.

(e) Substantially similar mixtures

Given:

(i) two mixtures: (A + B) and (C + B);

(ii) the concentration of ingredient B is essentially the same in both mixtures;

(iii) the concentration of ingredient A in mixture (A + B) equals that of ingredient C in mixture (C + B); and

(iv) data on toxicity for ingredients A and C are available and substantially equivalent; that is they are in the same hazard category and are not expected to affect the toxicity of ingredient B; then

if mixture (A + B) has already been classified by testing, mixture (C + B) can be assigned the same category.

(f) Aerosols

A hazard classification may be assigned for specific target organ toxicity (single or repeat exposure) for aerosols. Although in many cases, data are available only from repeat-dose oral studies, classification for specific target organ toxicity is dependent on the internal dose of a substance. Unless data are available for each component in an aerosol classified as 6.9 to confirm that the dermal and inhalation routes are not relevant, they cannot be excluded. When the propellant is not excluded, the propellant is taken into consideration for classification. If data are available to exclude the inhalation route for an aerosol, then the propellant is not taken into consideration.

17.3.3 Classification of mixtures when data are available for all or some ingredients of the mixture

When there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredients. In this case, the mixture will be classified as a specific target organ or systemic toxicant (specific organ specified), following single exposure and/or repeated exposure, when at least one ingredient has been classified as a 6.9A or 6.9B specific target organ or systemic toxicant and is present at or above the appropriate cut-off value or concentration limit as mentioned in Table 17.3 for 6.9A and 6.9B respectively.

Table 17.3: Cut-off values or concentration limits of ingredients of a mixture classified as a specific target organ or systemic toxicant that would trigger classification of the mixture.

	Cut-off or concentration limits triggering classification of a mixture as category	
Ingredient classified as category	**6.9A**	**6.9B**
6.9A Target organ or systemic toxicant	≥ 10%	≥ 1 but < 10%
6.9B Target organ or systemic toxicant	–	≥ 1%

Note: The cut-off values or concentration limits in the table apply to solids and liquids (by weight) as well as gases (by volume).

These cut-off values and consequent classifications should be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

Care should be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause specific target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

[The next page is page 17—63]

Appendix 17A: Acceptable test methods for specific target organ toxicity (single or repeated exposure)

17A.1 Introduction

Most of the guidelines mentioned in this appendix are found in compilations from the organisation issuing them. The guidelines listed below are not exclusive. If data have been generated using other valid international guidelines, then the results from those tests may also be applicable.

The main references to international guidelines referred to in this appendix are as follows.

- European Commission (EC) guidelines:

  European Commission 1996. *Classification, Packaging and Labelling of Dangerous Substances in the European Union. Part 2 – Testing Methods*. http://ecb.jrc.it/testing-methods Retrieved 14 August 2007.

- Organisation for Economic Co-operation and Development (OECD) guidelines:

  OECD 1993. *OECD Guidelines for the Testing of Chemicals*. Organisation for Economic Co-operation and Development, Paris, with regular updates. http://www.oecd.org/document/40/0,3343,en_2649_34377_37051368_1_1_1_1,00.html Retrieved 14 August 2007.

- United States Environmental Protection Agency (USEPA) Office of Prevention, Pesticides and Toxic Substances (OPPTS) guidelines:

  USEPA 2007. *Harmonized Test Guidelines*. United States Environmental Protection Agency. http://www.epa.gov/opptsfrs/home/guidelin.htm Retrieved 14 August 2007.

17A.2 Specific target organ toxicity test guidelines

The guidelines in Table 17A.1 are primarily relevant to substances that are, or solely contain, chemical substances. However, the Hazardous Substances and New Organisms Act 1996 also covers biopesticides that include micro-organisms. More specialised test methods may be required to adequately characterise the potential effects of biopesticides in mammals.

For testing microbial biopesticides, see the USEPA website for specific tests.

- USEPA 2007. *OPPTS Harmonized Test Guidelines: Series 885 Microbial Pesticide Test Guidelines – Final Guidelines*. Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency. http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/885_Microbial_Pesticide_Test_Guidelines/Series Retrieved 14 August 2007.

See also Table 17A.1.

Table 17A.1: Specific target organ toxicity (single or repeated exposure) test guidelines for chemicals, including mixtures

Test protocols	Test guideline		
	OECD	**EC**	**USEPA OPPTS**
Chronic toxicity	452	EC B.30 Chronic toxicity test	870.4100
Combined chronic toxicity and carcinogenicity	453	EC B.33 Combined chronic toxicity/carcinogenicity test	870.4300
90-day oral toxicity	408	EC B.26 Subchronic oral toxicity test: repeated dose 90-day study in rodents	870.3100
Subchronic non-rodent oral toxicity	409	EC B.27 Subchronic oral toxicity test: repeated dose 90-day study in non-rodents	870.3150
Repeated dose oral toxicity – 28 days	407	EC B.7 Repeated dose (28 days) toxicity (oral)	870.3050
Repeated dose dermal toxicity – 28 days	410	EC B.9	870.3200
Repeated dose inhalation toxicity – 28 days	412	EC B.8 Repeated dose (28 days) toxicity (inhalation)	–
Subchronic dermal toxicity	411	EC B.28 Subchronic dermal toxicity test: 90-day repeated dermal dose study using rodent species	870.3250
Subchronic inhalation toxicity	413	EC B.29 Subchronic inhalation toxicity test: 90-day repeated dermal dose study using rodent species	870.3465
Delayed neurotoxicity of organophosphorous substances – acute and 28 day	418 419	EC B.37 Delayed neurotoxicity of organophosphorus substances following acute exposure EC B.38 Delayed neurotoxicity of organophosphorus substances 28-day repeated dose study	870.6100
Neurotoxicity screening battery	–	–	870.6200
Developmental neurotoxicity study	–	–	870.6300
Schedule-controlled operant behaviour	–	–	870.6500
Peripheral nerve function	–	–	870.6850
Neurophysiology: sensory evoked potentials	–	–	870.6855
Companion animal safety	–	–	870.7200
Toxicokinetics	417	EC B.36: Toxicokinetics	870.7485
Dermal penetration	–	–	870.7600
Immunotoxicity	–	–	870.7800

Note: Data from reproductive or developmental toxicity studies may be used when specific target organ effects are found in parental animals, particularly when data are sparse from other studies.

[The next page is page 17—85]

Appendix 17B: Conversion of parts per million in the diet per day to milligrams of the substance per kilogram of bodyweight per day

Use Table 17B.1 to convert data from repeat-dose studies with the substance in the diet per day to milligrams of the substance per kilogram of bodyweight per day.

Table 17B.1: Approximate relation of concentration of the substance in the diet (ppm) to dietary intake (mg/kg bw/day)

Animal	Weight (kg)	Food consumed per day (g)	Type of diet	One ppm in food = mg/kg bw/day	One mg/kg bw/day = ppm of diet
Mouse	0.02	3	Dry laboratory chow diets	0.150	7
Chick	0.4	50		0.125	8
Rat (young)	0.1	10		0.100	10
Rat (old)	0.4	20		0.050	20
Guinea pig	0.75	30		0.040	25
Rabbit	2.0	60		0.030	33
Dog	10.0	250		0.025	40
Cat	2	100	Moist, semi-solid diets	0.050	20
Monkey	5	250		0.050	20
Dog	10	750		0.075	13
Man	60	1,500		0.025	40
Pig or sheep	60	2,400	Relatively dry grain forage mixtures	0.040	25
Cow (maintenance)	500	750		0.015	65
Cow (fattening)	500	15,000		0.030	33
Horse	500	10,000		0.200	50

Notes

- g = gram; kg = kilogram; mg/kg bw/day = milligrams of the substance per kilogram of bodyweight per day; ppm = parts per million.
- The values in this table are average figures derived from numerous sources.

Source: Adapted from IPCS (1990), originally from Lehman (1954).

17B.1 Example

Question: What is the value in parts per million (ppm) and mg/kg bw/day of 0.5% substance X mixed in the diet of an adult rat?

Answer: 0.5% corresponds to 5,000 ppm and from Table 17B.1 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg bw/day. Consequently, 5,000 ppm is equivalent to 250 mg/kg bw/day (that is, 5,000 × 0.05).

References

IPCS 1990. *Principles for the Toxicological Assessment of Pesticides Residues in Food*, Environmental Health Criteria 104. International Programme for Chemical Safety.

Lehman, AJ 1954. *Association of Food and Drug Officials Quarterly Bulletin* 18: 66.

[The next page is page 17—107]

Appendix 17C: Comparison of Globally Harmonized System of Classification and Labelling of Chemicals and HSNO Act specific target organ toxicity (single or repeated exposure)

Table 17C.1 and Table 17C.2 compare the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (United Nations, 2007) classifications for specific target organ toxicity (single or repeated exposure) and Hazardous Substances and New Organisms Act 1996 (HSNO Act) subclass 6.9 classification.

Note that the GHS assigns separate classifications for substances causing specific target organ toxicity, depending on whether this occurred from single exposure or repeat exposure. The HSNO Act classifications for this subclass can be assigned from either single or repeat exposure.

Table 17C.1: Comparison of Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and HSNO Act specific target organ toxicity (single exposure)

GHS specific target organ toxicity single exposure classification	HSNO Act equivalent category
Category 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following a single exposure Placing a substance in category 1 is done on the basis of: • reliable and good quality evidence from human cases or epidemiological studies; or • observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations (guidance dose–concentration values are used as part of the weight-of-evidence evaluation).	6.9A
Category 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following a single exposure Placing a substance in category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose–concentration values are used to help in classification. In exceptional cases, human evidence can also be used to place a substance in category 2.	6.9B
Category 3: Transient target organ effects There are target organ effects for which a substance or mixture may not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects that adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category includes only narcotic effects and respiratory tract irritation. Substances or mixtures may be classified specifically for these effects.	No equivalent

Note: For these categories, the specific target organ or system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general systemic toxicant. Attempts should be made to determine the primary target organ of toxicity and classify for that purpose (for example, hepatoxicants and neurotoxicants). One should carefully evaluate the data and, where possible, not include secondary effects (for example, a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal system).

Table 17C.2: Comparison of Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and HSNO Act specific target organ toxicity (repeat exposure)

GHS specific target organ toxicity repeat exposure classification	HSNO Act equivalent category
Category 1: Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure Placing a substance in category 1 is done on the basis of: • reliable and good quality evidence from human cases or epidemiological studies; or • observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose–concentration values are used as part of the weight-of- evidence evaluation.	6.9A
Category 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure Placing a substance in category 2 is done on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose–concentration values are provided to help in classification. In exceptional cases, human evidence can also be used to place a substance in category 2.	6.9B

Note: For both categories, the specific target organ or system that has been primarily affected by the classified substance may be identified, or the substance may be identified as a general systemic toxicant. Attempts should be made to determine the primary target organ of toxicity and classify for that purpose (for example, hepatoxicants and neurotoxicants). One should carefully evaluate the data and, where possible, not include secondary effects (for example, a hepatotoxicant can produce secondary effects in the nervous or gastrointestinal system).

References

United Nations 2007. *The Globally Harmonized System of Classification and Labelling of Chemicals (GHS)*, 2nd revised edition. United Nations, Geneva.

[The next page is page 17—129]

Appendix 17D: Comparison of European Union specific target organ toxicity risk phrases with HSNO Act specific target organ toxicity

The European Union (EC, 1967) risk phrases are converted into the equivalent Hazardous Substances and New Organisms Act 1996 (HSNO Act) classification in Table 17D.1.

Table 17D.1: Comparison of European Union specific target organ toxicity risk phrases with HSNO Act equivalent classification specific target organ toxicity

European Union risk phrases	HSNO Act equivalent category
Very Toxic (T+) A substance is determined to be hazardous and classified as Very Toxic (T+) and assigned one of the following risk phrases in accordance with the criteria given below.	
R39 Danger of very serious irreversible effects Strong evidence that irreversible damage, other than the carcinogenicity, mutagenicity and reproductive effects referred to below, is likely to be caused by a single exposure in the dose ranges used for classification as being Very Toxic (T+) by different routes; that is: • inhalation LC_{50} rat, for aerosols or particulates: ≤ 0.25 mg/L over 4 hours; • inhalation LC_{50} rat, for gases and vapours: ≤ 0.5 mg/L over 4 hours; • dermal LD_{50} rat or rabbit; ≤ 50 mg/kg; • oral LD_{50} rat ≤ 25 mg/kg.	6.9A
Toxic (T) A substance is determined to be hazardous and classified as Toxic (T) and assigned one or more of the following risk phrases in accordance with the criteria given below.	
R39 Danger of very serious irreversible effects Strong evidence that irreversible damage other than carcinogenicity, mutagenicity and reproductive effects, is likely to be caused by a single exposure by an appropriate route. Substances are classified at least as Toxic (T) when these effects are observed at acutely toxic dose levels, that is: • inhalation LC_{50} rat, for aerosols or particulates: 0.25 < LC_{50} ≤ 1 mg/L over 4 hours; • inhalation LC_{50} rat, for gases and vapours: 0.5 < LC_{50} ≤ 2 mg/L over 4 hours; • dermal LD_{50} rat or rabbit: 50 < LD_{50} ≤ 400 mg/kg; • oral LD_{50} rat: 25 < LD_{50} ≤ 200 mg/kg.	6.9A
R48 Danger of serious damage to health by prolonged exposure (not acute) Serious damage (clear functional disturbance or morphological change that has toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. Substances are classified at least as Toxic (T) when these effects are observed at the following dose ranges: • inhalation, rat ≤ 0.025 mg/L, 6 hours/day; • oral, rat ≤ 5 mg/kg bw/day; • dermal, rat or rabbit ≤ 10 mg/kg bw/day.	6.9A Note the inhalation cut-off also crosses into 6.9B

European Union risk phrases	HSNO Act equivalent category
Harmful (Xn) A substance is determined to be hazardous and classified as Harmful (Xn) and assigned one or more of the following risk phrases in accordance with the criteria given below.	
R48 Danger of serious damage to health by prolonged exposure Serious damage (clear functional disturbance or morphological changes that have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route. Substances are classified at least as Harmful (Xn) when these effects are observed at the following dose ranges: • inhalation, rat ≤ 0.25 mg/L, 6 hours/day; • oral, rat ≤ 50 mg/kg bw/day; and • dermal, rat or rabbit ≤ 100 mg/kg bw/day. These guide values can apply directly when severe lesions have been observed in a subchronic (90 days) toxicity test. As a guideline, when interpreting the results of a sub-acute (28 days) toxicity test these figures should be increased at least threefold. If a chronic (two years) toxicity test is available, it should be evaluated on a case-by-case basis. If results of studies of more than one duration are available, then those from the study of the longest duration should normally be used.	6.9A

Notes: bw = bodyweight; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; mg/kg = milligrams per kilogram; mg/L = milligrams per litre.

Source: EC (1967).

References

EC 1967. General classification and labelling requirements for dangerous substances and preparations. *Council Directive 67/548/EEC of 27 June 1967 on the Approximation of Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Substances*. European Commission, Annex VI. http://ec.europa.eu/environment/dansub/consolidated_en.htm.